Clinical Update

Naval Postgraduate Dental School
Navy Medicine Personnel Development Center
8901 Wisconsin Ave
Bethesda, Maryland 20889-5602

Vol. 35, No. 1 April 2013

Human Papillomavirus-associated Head and Neck Squamous Cell Carcinoma

Major Heather Olmo, DC, USA, Captain Robert D. Foss, DC, USN
and Commander Marc Stokes, DC, USN

Introduction

Head and neck squamous cell carcinoma (HNSCC) which includes the oral cavity, oropharynx and larynx is the sixth most common cancer worldwide with an estimated 633,000 incident cases and 335,000 deaths annually[1,2]. Human papillomavirus (HPV) is specifically associated with squamous cell carcinomas (SCC) of the oropharynx which encompasses the base of the tongue, lingual and palatine tonsils and the pharyngeal walls. This is in contrast to conventional HNSCC which typically involve the oral cavity proper (mostly tongue and floor of mouth) or the larynx. The significant role of HPV in HNSCC is a rapidly advancing area of medicine [3] and HPV-associated oropharyngeal SCC (HPV-SCC) can now be considered a distinct clinical entity. Currently, nearly 150 HPV types have been identified and 120 of these have been fully DNA sequenced [4]. HPV types 16 and 18 are the primary 'high-risk' types that are most frequently associated with HPV-SCC. It should be noted that HPV 16 and 18 are well established causative agents of cervical cancer. HPV 16 accounts for the majority (87%) of HPV-positive cases of HNSCC [1].

Epidemiology

There has been a progressive increase in the incidence of HPV-SCC over the past two decades and the trend is expected to continue [1,2]. Compared to conventional HNSCC, HPV-SCC is characterized by a younger age of onset, an association with sexual behaviors and improved survival [1,5]. Natural history and case-control studies have shown that cervical carcinoma is a sexually transmitted disease and strongly suggest a similar etiology for HPV-SCC [1,2,6]. An increased number of sexual partners is the principal risk factor for HPV-SCC in contrast to conventional HNSCC, for which tobacco and alcohol remain the principal risk factors [1,2,6,7]. In case-matched comparisons, the sexual behaviors of patients with HPV-SCC were significantly different from those reported by HPV-negative cases with regard to the number of lifetime sexual partners [7]. There was a significant correlation between increasing numbers of sexual partners and an increased incidence of HPV-positive SCC. Studies also suggest that alcohol and tobacco use may have synergistic effects with HPV in HPV-SCC [7].

HPV-SCC is epidemiologically, biologically and clinically distinct from HPV-negative tumors, and therefore has differing clinical and prevention implications [1,2]. HPV-induced carcinogenesis is characterized by molecular events that are predominantly modulated through expression of the E6 and E7 viral oncogenes. E6 binds to p53 tumor-suppressor protein while E7 binds retinoblastoma tumor-suppressor protein (pRb) causing inactivation and stimulating their degradation [4]. This binding is the key to the induction of carcinogenesis.

Diagnosis

The diagnosis of HPV-SCC is made on the basis of clinical presentation and pathology [8]. Clinically, a unilateral tonsil (tonsillar asymmetry) or base of tongue mass should be considered highly suspicious for HPV-SCC. Because the carcinomas originate from tonsil crypt epithelium it is not uncommon for patients to present with metastatic disease and an occult primary tumor. In these cases a lateral neck mass, representing lymph node metastasis, may be the initial sign of disease. These neck masses are frequently cystic in nature and histologic examination is required for diagnosis. Morphologically, HPV-SCC has a characteristic appearance that sets it apart from conventional HNSCC. The surface epithelium may not demonstrate the dysplasia that is seen in most conventional HNSCC. The tumor is composed of invasive islands of basaloid cells that frequently exhibit central comedonecrosis [8]. Keratinization is for the most part absent or only focally identified [8]. HPV-SCC is usually designated as non-keratinizing squamous cell carcinoma [8]. Ancillary laboratory studies should be performed to confirm the presence of HPV[9]. In-situ hybridization for high risk HPV is acceptably specific and sensitive while immunohistochemical staining for p16, a surrogate HPV marker, is very sensitive [9,10].

Treatment and Prognosis

Once the diagnosis of HPV-SCC has been established, treatment typically consists of surgery, chemotherapy, radiation therapy or combinations thereof. HPV-SCC has been shown to have a better prognosis when compared with conventional HNSCC. The three-year survival rate for HPV-SCC approaches 71% compared to 46% in conventional HNSCC [1,5]. In other studies, HPV-SCC had a 28% reduction in the risk of death and a 49% reduction in the risk of disease recurrence [1,2,5]. Molecular changes, such as TP53 mutations and epithelial growth factor receptor (EGFR) over-expression, are thought to be associated with a worse prognosis in HNSCC. HPV-SCCs harbor fewer TP53 mutations which may be a

prognostic factor. It has also been speculated that immune responses to HPV antigens (E6/E7 proteins) have contributed to superior survival rates for HPV-SCC [1,5]. The precise mechanism responsible for the more favorable prognosis of HPV-SCC is still unclear [1].

Conclusion

HPV-SCC and conventional HNSCC are epidemiologically and genetically distinct. Additionally, therapeutic response and survival is more favorable in HPV-SCC. Currently there is no single standard treatment protocol for HPV-SCC. Continued research into the molecular mechanisms of HPV-SCC is essential for the potential design of molecular targeted treatment strategies and in the development of specific treatment protocols for HPV-SCC.

References

1. Chaturvedi AK. Epidemiology and clinical aspects of HPV in head and neck cancers. Head Neck Pathol. 2012;6 Suppl 1:S16-S24.
2. Adelstein DJ, Ridge JA, Gillison ML, Chaturvedi AK, D'Souza G, Gravitt PE, Westra W, Psyrri A, Kast WM, Koutsky LA, Giuliano A, Krosnick S, Trotti A, Schuller DE, Forastiere A, Ullmann CD. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9-10, 2008, Washington, D.C. Head Neck. 2009;31(11):1393-1422.
3. Lewis JS Jr. Introduction: Human papillomavirus in head and neck cancer: an update for 2012 with a focus on controversial topics. Head Neck Pathol. 2012;6 Suppl 1:S1-S2.
4. Rautava J, Syrjänen S. Biology of human papillomavirus infections in head and neck carcinogenesis. Head Neck Pathol. 2012;6 Suppl 1:S3-S15.
5. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul 1;363(1):24-35.
6. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol 2010;39:166–181.
7. Smith EM, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Tobacco and alcohol use increases the risk of both HPV-associated and HPV-independent head and neck cancers. Cancer Causes Control. 2010;21(9):1369-1378.
8. El-Mofty SK, Zhang MQ, Davila RM. Histologic identification of human papillomavirus (HPV)-related squamous cell carcinoma in cervical lymph nodes: a reliable predictor of the site of an occult head and neck primary carcinoma. Head Neck Pathol. 2008 Sep;2(3):163-8.
9. Venuti A, Paolini F. HPV detection methods in head and neck cancer. Head Neck Pathol. 2012 Jul;6 Suppl 1:S63-S74.
10. Lewis JS Jr. p16 Immunohistochemistry as a standalone test for risk stratification in oropharyngeal squamous cell carcinoma. Head Neck Pathol. 2012;6 Suppl 1:S75-S82.

Major Heather Olmo (USA) is an oral and maxillofacial pathology resident. Captain Robert Foss (USN) is the Oral and Maxillofacial Pathology Residency Program Director, Naval Postgraduate Dental School. Commander Stokes (USN) is the Department Chairman, Oral and Maxillofacial Pathology.